## REMARKS

Amendments to the Claims

Claims 9-16 have been canceled. New Claims 21-22 have been added. Support for Claims 21-22 can be found page 6 lines 26-27. No new matter has been added as a result of this amendment.

Double Patenting

The Examiner has rejected Claims 1-16 for Obviousness-Type Double Patenting over Claims 2-7 of the U.S. Patent No. 6,368,877. In order to obviate the rejection, Applicants are concurrently filing a Terminal Disclaimer in compliance with 37 C.F.R. §1.132(c) over the cited patent.

The Examiner has provisionally rejected Claims 1-16 for Obviousness-Type Double Patenting over Claims 1-6 of the copending U.S. Patent Application No. 10/317,838. U.S. Patent Application No. 10/317,838 has been abandoned, thereby rendering the rejection moot.

Claim Rejections 35 USC § 112 second paragraph

The Examiner stated that Claim 1-16 are rejected under 35 USC § 112, as the term "predetermined" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants respectfully disagree. As defined in Webster's New Twentieth Century Dictionary 2nd Ed. predetermined means:

1. to determine, decide or decree beforehand.

A copy of this definition is attached as Exhibit A.

The term "predetermined", in the instant claims, means that the "pattern" was ***known***, ***decided*** or ***designed prior to*** fabricating the pattern. The design of the pattern is not critical, but rather the ability to design a pattern of self-assembled monolayers to achieve a specific purpose. Page 10 lines 24 through page 11 line 2 reads:

> The patterns which can be selected in this invention are not particularly critical. Preferred patterns for SAMs useful as research tools in the study of cell/cell interactions are linear tracks of alternating peptides which can adhere to the cells and inert tracks of solid support or an inert compound bound to the solid support. Depending upon the thickness of the tracks, the orientation of the cell can further be manipulated. That is a thin track can results in the orientation of the cells linearly.

As such the pattern can be designed for a specific purpose prior to fabrication of the pattern. If the pattern is known or designed prior to fabrication, it is implied that the pattern design can be reused or reproduced.

The term "pre-determined", excludes any pattern formed by the spontaneous orientation of the peptide on a uniform surface. The following statement on page 10 lines 14-23 of the specification makes it clear that a feature of the invention is that the peptides are distributed on a surface in a specific pattern and are not distributed randomly or homogenously:

> The peptides are printed on the solid support, as will be described below. The terms "printed", "patterned" or "predetermined pattern" are defined herein to mean that the solid support has ordered areas where the peptides are bonded and not bonded to the solid support. That is, a printed or patterned solid support is expressly not intended to include a support with a random or substantially homogenous distribution of the peptide over its entire surface(s).

The term "pre-determined" as written is clear. It can be determined if a pattern was pre-determined if the pattern is not a random or homogenous distribution of the peptide over the entire surface, but rather that peptide is arranged in ordered areas to form a pattern which was ***known*** or ***designed prior to*** fabrication of the pattern.

The Examiner has stated that Claim 13 recites an improper Markush group. Claim 13 has been canceled and the rejection is now moot.

Claim Rejections 35 USC § 112 first paragraph

Claim 1-8 and 14 are rejected under 35 USC § 112 first paragraph for allegedly failing to comply with the written description requirement. In making the rejection, the Examiner states that the claims are drawn to compositions comprising linear peptides that specifically bind to a cell surface protein. The Examiner complains that the claims do not require that the peptide possess any particular amino sequence, conserved structure or other distinguishing feature. For reasons provided below Applicants' respectfully disagree with the rejection.

The instant claims comprise a presenting group which binds specifically to a cell surface protein. The presenting groups are described on page 6 lines 9-11:

> For example, where the target is a cell, the target molecule can be a cell surface protein. The presenting group can be a ligand for that protein, antibody or an antigen-binding fragment thereof which binds specifically to the cell surface protein.

Examples of suitable presenting groups are defined page 6 lines 15-23:

> Particularly suitable presenting groups are oligopeptides which self assemble to form a beta sheet under conditions for the desired or selected application. Examples of oligopeptides which self assemble under these conditions are described in United States Application Serial Nos. 08/346,849 and 08/784,606, which are incorporated herein by reference in their entireties. Briefly, these oligopeptides are amphiphilic, have alternating hydrophobic and hydrophilic amino acids and are complementary. As will be described in more detail below, particularly preferred oligopeptides for self assembly are $RADX_n$ and $EAKX_n$ wherein X is an amino acid and n is an integer between about 2 and about 8.

The peptides of the present invention are linear. Suitable linear peptides are described in detail from page 3 lines 35 through page 5 line 25. Methods of manufacturing the peptides are described page 9 lines 3-13. The central linker is between about 2 to about 30 amino acids in length, more preferably between 2 and about 8 amino acids. There are a finite number of amino acids known in the art which when combined would result in the formation of a linear peptide.

Suitable amino acids for this purpose are listed page 5 lines 19-22, and include, glycine, L-alanine, and D-alanine. Based on the teachings of the instant specification, one of skill in the art could readily design a linear peptide which meets the limitations of the instant claims. In light of this Applicants' have provided adequate written description for one skilled in the art to envision a linear peptide of about 2 to about 30 amino acids in length within the scope of the instant claims.

With respect to the linker, the only requirement is that it be an oligopeptide which does not interfere with the activity of the presenting group. Because one of ordinary skill in the art can immediately envision a multiple of such linking groups there is no written description issue with respect to the central linker.

Further, the Examiner correctly states that cell surface proteins which are suitable target molecules include CD4, CD8 neuronal cell surface receptors including NC-Cams, L1 receptors, NGF receptors, netrin receptors and others. With this long list the Examiner is implicitly recognizing that the field of cell surface receptors is well developed, and that many motifs, i.e., "presenting groups", for these cell surface receptors were known at the time the subject application was filed. It is axiomatic that an application need not describe, and indeed, preferably omits, what is already known to one of ordinary skill in the art. As such, the recitation of SEQ ID Nos. 2-5 are merely exemplary. There is no written description issue because one of ordinary skill in the art already knows of many suitable presenting groups.

It is also noted that Applicant's invention is not based on the identification of new presenting groups, which as discussed, are already well characterized. Rather, the use of these known groups to prepare a new composition with a new utility, the ability to specifically bind cell types which uniquely bind a cell surface protein. As such, the citation of Prieto *et al.* does not support the Examiner's position. Enough presenting groups were known already at the time of filing for one of ordinary skill in the art to practice the invention. Therefore, the written description has been satisfied, even if some presenting groups have not yet been characterized. Withdrawal of the rejection is respectfully requested.

The Examiner also alleges lack of adequate description for "pre-determined pattern". As discussed above, a "predetermined pattern" is a pattern which was ***known*** or ***designed prior to*** the making the pattern. Based on the teachings on the instant specification, a pattern is pre-determined if the pattern is not a random or homogenous distribution of the peptide over the entire surface, but rather that peptide is arranged in ordered areas to form a pattern which was ***known*** or ***designed prior to*** fabrication of the pattern.

The Examiner further states that claims 1-8 and 14 are rejected under 35 USC § 112 as the specification does not reasonably provide enablement for immobilizing any cell surface protein or target molecule using any monolayer of linear peptides

The Examiner has applied the analysis *In re Wands* while analyzing the state of the prior art and predictability in the art.

The burden is on the Examiner to establish a reasonable basis to establish lack of enablement:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d, 1557, 1562, 27 USPQ2d 1510, 1531 (Fed .Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented mist be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367 , 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370. MPEP 2164.04.

The Examiner has merely asserted that it is unpredictable that a particular peptide motif capable of cell adhesion function similarly in all species.

As discussed above, Applicants' invention is not based in the identification of new presenting groups. As discussed in the section of this paper responding to the written description rejection, a multitude of target cell surface receptors and their corresponding binding motifs (i.e., presenting groups) were known at the time the subject application was filed. One skilled in the art does not need to investigate all presenting groups to practice the Applicant's invention. Rather, Applicant's invention utilizes known presenting groups, specific for cell surface proteins, to prepare a new composition with a new utility. This new utility is the ability to specifically bind a cell surface protein, thereby capturing the cell onto the SAM.

Applicant's have demonstrated (Example 1, page 19 lines 9-13) that the peptide $(RADC)_3$ AAAC (SEQ ID NO: 1) when bound to a solid support in the form of a self-assembled monolayer can target and immobilize specific cells. This Example demonstrates that using the composition of the invention, which is a self-assembled monolayer of linear peptides bound to a solid surface with a known presenting group, it is possible to immobilize a specific cell in a pre-determined pattern on a surface. This cell is immobilized on the surface based on the interaction with the presenting group. It is therefore reasonable to conclude that the RADC peptide can be replaced with another known presenting group, in the composition of the invention, to immobilize a target cell on a surface. Indeed, the Examiner has presented no reason to the contrary. If the Examiner doubts this assertion, it is requested that he provide evidence of his reasoning.

Therefore based on the teachings of the instant specification one of ordinary skill in the art would readily be able to design and produce a self-assembled monolayer of linear peptides which falls within the scope of the instant claims. Withdrawal of the rejection is respectfully requested.

Claim Rejections- 35 USC § 102

Claims 1-5 and 9-15 are rejected under 35 USC § 102 (b) as being anticipated by Mrksich *at al.* The Examiner states that Figure 2, teaches patterned adsorption of proteins on surfaces and page 229 paragraph 5 through page 230 paragraph 4 teaches protein adsorption of proteins onto SAMs (taken as the bonding of an amino terminus of a polypeptide to a surface).

Claims 1-5 are directed to self-assembled monolayers comprising linear peptides bonded to a solid support. In contract, Mrksich *et al.* teach self-assembled monolayers of alkanethiols attached to a solid support (Abstract page 228):

> Self-assembled monolayers (SAMs), formed upon the adsorption of ω-substituted alkanethiols on the surface of gold, allow control of the properties of a surface on the molecular scale.

Mrksich *et al.* do not teach a self-assembled monolayer of linear peptides, as required by Claim 1. Thus the instant claims are structurally distinct and therefore novel in light of Mrksich *et al.*

It is acknowledged that Mrksich *et al.* discloses adsorbing proteins onto the alkanethiol groups of the SAMs. For example, Figure 2 of Mrksich *et al.* shows an alkanethiol self-assembled monolayer with proteins adsorbed onto the SAM. Similarly, Figure 6 shows a His-tagged receptor cell attached to a SAM. Thus, the peptides are attached to the alkanethiol SAM and ***not to*** the solid support.

In contrast, the instant claims require that the linear peptides be bound to the solid support by a bond between the solid support and a terminal amino acid of the linear peptide.

It appears that the Examiner has interpreted the "solid support" in Claim 1 to encompass "surface" as that term is used in Mrksich *et al.* "Surface" in Mrksich *et al.* refers to the solid support and the alkanethiol bonded thereto. Applicants do not, however, agree that "solid support" in Claim 1 encompasses "surface" as used in Mrksich *et al.*. The composition of the solid support is defined in the specification page 9 lines 23-27:

> For example, the solid support can be an inorganic material such as a metal, including as gold, copper, zinc, silver or nickel or metal alloy. Alternatively, the solid support can be glass, silica, or silicon oxide. In yet another embodiment, the solid support can be an organic material, such as a polymer or resin, including nylon, poly(ethylene glycol), and polyfluoropolymers.

The definition of solid support in the instant Application does not include a self-assembled monolayer of alkanethiols attached to a solid support. Thus Claims 1-5 are structurally distinct and therefore novel in light of Mrksich *et al.* reconsideration and withdrawal of the rejection are respectfully requested.

Even if "solid support" in Claim 1 is interpreted as encompassing a solid support with an alkanethiol bonded thereto, Claim 1 is still novel in view of Mrksich *et al.* In Mrksich *et al.* the proteins are attached to the alkanethiol. However, the interactions are non-specific, i.e., the interactions occurring between the alkanethiol and the surface of the protein. There is no bond between the ***terminal amino acid*** of the protein and the alkanethiol or the solid support, as required by Claim 1. Therefore, the subject matter of Claim 1 is still novel in view of Mrksich *et al.*

Claims 1, 2, 4, 6, 7, 9, 10, 13 and 14 are rejected under 35 USC § 102 (b) as being anticipated by Pirrung *et al.* and Claims 1, 4-7, 9 and 12-16 are rejected under USC § 102 (b) as being anticipated by Holmes.

Applicants' Invention

Applicants' SAMs contain peptides bound to a surface in a predetermined pattern which allows the target, i.e., the specific cell, to bind to the peptides assembled at a particular locus on a surface. Thus, Applicants' SAMs have the important advantage of being able to select cells of a certain type and bind them in a desired pre-determined pattern. There are many advantages to binding cells in a pre-determined pattern, as opposed to binding them in random patterns. Examples of such advantages are disclosed in the specification page 17 lines 10- 14:

> The invention permits very accurate control of cell population and density. The invention can be utilized to study cell growth and cellular interactions to external stimuli, including other cells, growth factors, repellants and inhibitors. Thus, the invention represents a significant advance in the ability to conduct research in biology and medicine.

Further Applicants' SAMs can be useful in assays such as studies involving the formation of connections between cells, such as neurons (page 17 line 26 through page 18 line 8):

> The understanding of complex neuronal connections is central to our comprehension of central nervous system function, and advances in doing so will benefit from combining engineering with molecular cell biology to analyze neuronal behavior under well-characterized and controlled conditions. Neurite outgrowth, guidance and connections can be studied on surfaces patterned with self-assembling peptides that contain cell-adhesion motifs. Controlling neurite outgrowth, including distances, angles and direction, can be important in controlling and studying synapse formation between neuronal cells guided into proximity. Neuronal cells attached to the described SAMs can be employed in the study of neuronal cell culture, synapse formation, neuronal connection engineering, screening neuropeptides, as well as pharmaceutical agents that stimulate, inhibit or alter the nature of nerve growth, and inter-connections.

Applicants' invention solves the problem of binding specific cells to a peptide SAM that has a pre-determined pattern and specificity for a particular protein on the membranes of the cells. Applicants solved this problem by utilizing a printed SAM formed from peptides that are bound to the solid support at one of the terminus of the peptides. In addition, the peptides have a ligand at the other terminus with a particular motif that binds specific proteins. As a result, cells expressing those proteins in the cell membrane are bound to the SAM in the desired pattern.

Response to the Rejection

Pirrung *et al.* and Holmes teach screening methods to determine the biological activity of a variety of known peptide sequences, for example, to determine a sequence which mimics an antigenic epitope. The objective of Pirrung *et al.* and Holmes is to identify peptides which bind to macromolecules, including cell surface receptors, see Pirrung *et al.* column page 8 lines 34-38:

> The prepared substrate may, for example, be used in screening a variety of polymers as ligand for binding with a receptor, although it will be apparent that the invention could be used for the synthesis of a receptor.

This is accomplished by attaching peptides to a surface and then assessing whether surface bound peptides bind the receptor. The sequence of the surface bound peptide is varied to determine which sequence or which groups of sequences bind the target molecule.

Identifying peptides which specifically bind the receptor is not an objective of Pirrung *et al.* or Holmes. By "specifically bind" it is meant that the peptide binds the target receptor to a significantly greater degree than other receptors. It is not known whether any peptides identified by the methods of Pirrung *et al.* or Holmes specifically bind the target receptor, and indeed, it is not possible to determine by the methods described in Pirrung *et al.* or Holmes whether the binding is specific. Finally it is well established that many peptides which bind macromolecules, such as, the receptors defined in Pirrung *et al.* and Holmes, bind other macromolecules to a significant extent, i.e., they are non-specific.

Claims 1, 2, 4, 6 and 7 require that the presenting groups is specific for one cell surface protein. As discussed above Pirrung *et al.* and Holmes do not teach peptides which are ***specific*** for one particular cell surface protein. That is, Pirrung *et al.* and Holmes do not meet the requirements of Claim 1 that the presenting group specifically bind a cell surface protein. Hence the instant claims are novel in light of Pirrung *et al* and Holmes.

Claims 1, 9, 13 and 14 are rejected under USC § 102 (b) as being anticipated by Kauvar.

Claim 1 discloses a self-assembled monolayer of linear peptides bound in a pre-determined pattern to a solid support, wherein the linear peptides comprise a presenting group (which binds to a specific cell surface protein), a central linker and a terminal amino acid. Claim 1 requires that the peptide be bound to the solid support through a bond between the terminal amino acid and the solid support. Therefore, the interaction between the peptide and the

substrate is specific in the sense that the peptide is bound to the substrate at one specifically defined part of the peptide, i.e., at its terminus.

Kauvar discloses screening methods to identify a particular analyte by its pattern of binding strength to a panel of related antibodies and to match an arbitrary analyte with an immunoreactive member of a panel of candidate antibodies. The antibodies may be bound to a solid support in a patterned fashion.

Methods of immobilizing the antibodies are described in Kauvar in Example 2 column 26 lines 15-19, and the solid supports used are described in column 24 lines 27-46. Examples of solid supports used include activated membranes, such as, a commercially available derivatized agarose membrane: "NuFix™. These membranes contain reactive groups which react non-specifically and therefore form covalent bonds between the antibody and the membrane, which can be formed anywhere on the antibody surface. Hence the antibodies can be in a variety of orientations on the membrane surface. The compositions in Kauvar therefore do not satisfy the requirement of Claim 1, that the peptide be attached at its terminus to a substrate.

Kauvar does not teach or suggest binding the antibody to the surface at one specifically defined part of the antibody. Therefore Kauvar et al. do not teach a peptide bound to a solid support by a bond between the terminal amino acid and the solid support and hence the peptides disclosed in the instant claims are structurally distinct and therefore novel in light of Kauvar.

Claim Rejections- 35 USC § 103

Claims 1 and 5-8 are rejected under 35 USC § 103(a) as being unpatentable over any of Mrksich *et al.,* Pirrung *et al.* or Holmes each taken separately; and further in view of Schatz *et al.*

Claims 1 and 5-8 disclose a self-assembled monolayer (SAM) of linear peptides comprising a presenting group which binds to a specific cell surface protein, wherein the SAM is bound in a pre-determined pattern to a solid support via a bond between the terminal amino acid and the solid support.

The objective of Mrksich *et al.* is to immobilize a protein on a solid support using an alkanethiol SAM. Because the protein attaches to the alkanethiol, the interactions are non-specific i.e., the surface will bind proteins generally rather than one protein type specifically. Mrksich *et al.* do not solve the problem of the instant invention, which is to immobilize a specific cell at a specific locus on a pre-determined pattern of self-assembled monolayers of linear peptides. Mrksich *et al.* do not provide any advantages of replacing the alkanethiol with the protein, let alone replacing the protein with a peptide comprising a presenting group which binds a specific cell. In conclusion, there is no teaching or suggestion in Mrksich *et al.* to form self-assembled monolayers of linear peptides to bind a specific cell in a pre-determined pattern on a surface. The instant claims are therefore non-obvious in light of Mrksich *et al.*

The objective of Pirrung *et al.* or Holmes is to screen a variety of ligands to determine which if any bind to certain receptors. Pirrung *et al.* or Holmes do not require ligands which are specific for one cell surface protein, nor do they teach any advantages which could be achieved using ligands which are specific for certain cell surface proteins. Moreover, the instant invention solves the problem of capturing cells onto solid surfaces by utilizing presenting groups specific for receptors expressed on the surface of these cells (see Example 1). None of these references cited by the Examiner suggest the solution to this problem (using cell specific presenting groups). Moreover they provide no expectation that this solution would be successful.

One of ordinary skill in the art would not arrive at the instant invention following the teachings of Pirrung *et al.* or Holmes, thus the instant claims are non-obvious in light of Pirrung *et al.* and Holmes.

Schatz *et al.* disclose methods for constructing a random peptide library and screening methods using said peptide library. Schatz et al. further disclose the use of a spacer or linker molecule which is defined at Column 4 lines 6- 12:

> "Linker" or "spacer" refers to a molecule or group of molecules that connects two molecules, such as DNA binding protein and a random peptide, and serves to place two

molecules in a preferred configuration, with minimal steric hindrance from the DNA binding protein.

As noted, Mrksich *et al.*, Pirrung *et al.* or Holmes do not solve the problem of the instant invention as the do not teach or suggest utilizing peptides with a specific cell binding motif to immobilize cells at a certain locus on a patterned SAM. The combination of Schatz *et al.* does not remedy the deficiencies of Mrksich *et al.*, Pirrung *et al.* or Holmes as Schatz *et al.* does not teach or suggest utilizing peptides with a specific cell binding motif to immobilize cells at a certain locus on a patterned SAM. Thus the instant Claims 1 and 5-8 are non-obvious over any of Mrksich *et al.*, Pirrung *et al.* or Holmes in view of Schatz *et al.*

## CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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